Remarks

Reconsideration of this Application is respectfully requested.

Claims 6-17 are pending in the application, with 6, 12, 13, and 14 being the independent claims. Claims 6-10 and 12-14 are sought to be amended. Claims 6-10 and 12-14 are amended to remove non-elected embodiments of the invention. Claims 6 and 12-14 are further amended to more specifically claim the invention. Support for the amendments is found in the claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Summary of Examiner Interview

Applicants thank the Examiner and Supervisory Primary Examiner Woitach for the helpful interview on April 25, 2007. Applicants presented data regarding the differences between the ecdysone receptor binding activity of a compound and its ability to function as a gene switch activator. Applicants further presented data on the necessity of the right-hand carbonyl group of gene switch activator compounds for activity. Applicants also presented evidence that the compounds disclosed in Michelotti *et al.* are unlikely to function as gene switch activators. The Examiner indicated that the data was persuasive in showing that there was no suggestion or motivation in the prior art to make the claimed compounds. The Examiner indicated that the rejections would be

reconsidered when the data was filed in a declaration under 37 C.F.R. 1.132 together with a Request for Continuing Examination.

Rejections under 35 U.S.C. § 103

Claims 6-17 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Martinez *et al.*, (*Mol. Gen. Genet. 261*:546 (1999)), in view of both Dhadialla *et al.* (*Annu. Rev. Entomol. 43*:545 (1998)) and Saez *et al.* (*Proc. Natl. Acad. Sci. USA 97*:14512 (2000)), as evidenced by Guan *et al.* (*J. Combinatorial Chem. 2*:297 (2000)) and Michelotti *et al.* (U.S. Patent No. 5,304,572). (Office Action, page 2). Applicants respectfully traverse this rejection.

The Examiner alleges that Martinez *et al.* teach controlled gene expression systems involving chimeric receptors comprising the ligand binding domain of ecdysone receptors (EcRs) and also teach specific, dose-dependent activation in response to the non-steroidal EcR agonist RH5992. (Office Action, pages 4-5). The Examiner further alleges that Saez *et al.* teach ecdysone-regulated gene switches and disclose that a number of non-steroidal small molecules are capable of activating the ecdysone system. (Office Action, page 5). Based on the teachings of both Martinez *et al.* and Saez *et al.*, the Examiner is of the opinion that one of skill in the art would be motivated to search for more efficient, readily available non-steroidal EcR agonists. (Office Action, page 6).

Applicants respectfully disagree. Martinez *et al.* disclose that the non-steroidal EcR binding compound RH5992, a diacylhydrazine, functions as a gene switch activator in an EcR-based expression system. (Martinez *et al.*, page 549, column 1, first full paragraph). Saez *et al.* tested 21 different diacylhydrazine compounds (including

RH5992) in their EcR gene expression system and found that 9 out of the 21 compounds showed some potency as gene switch activators. (Saez *et al.*, page 14514, column 2, second full paragraph). These references, taken alone or together, teach that some (but not all) diacylhydrazine compounds that are able to bind the EcR are also capable of activating an EcR-based gene expression system. The references are absolutely silent regarding any teaching of any other compounds or structures that might be useful either for EcR binding or for gene switch activation. In fact, Saez *et al.* state that, in the absence of crystal structure studies, it is unclear what constitutes potent versus ineffective EcR ligands. (*Id.*, page 14513, column 2). Thus, these two references might, at best, suggest to one of ordinary skill in the art to randomly test other diacylhydrazine compounds for the ability to activate a gene switch, but they provide no motivation or guidance towards any other particular structures or compounds.

The Examiner next alleges that Dhadialla *et al.* disclose the compound 3,5-di-tert-butyl-4-hydroxy-N-isobutylbenzamide (DTBHIB) as an EcR agonist with potency similar to RH-5849, a known diacylhydrazine pesticide. (Office Action, page 6). The Examiner acknowledges that DTBHIB does not contain a ketone group that is a critical element of the claimed compounds. (Office Action, page 6). However, the Examiner is of the opinion that DTBHIB is very similar to the claimed compounds, having the same central core and both having EcR agonist activity, and that it is within the skills of the artisan to build combinatorial libraries around the central core by routine experimentation. (Office Action, page 6). The Examiner further states that, since building combinatorial libraries is a common procedure in the art for identifying variants with improved activity (as evidenced by Guan *et al.*), one of skill in the art would have

been motivated to modify the method of Martinez *et al.* by using DTBHIB or its derivatives because DTBHIB was proven to be an efficient EcR agonist. (Office Action, page 6).

Applicants respectfully disagree. The combination of Dhadialla et al. with Martinez et al. and Saez et al. would not produce the presently claimed invention. Dhadialla *et al.* provide a discussion of EcR ligands and their use as pesticides. Dhadialla *et al.* disclose the compound DTBHIB and its apparent ability to bind the EcR receptor. DTBHIB is not a diacylhydrazine, and is not encompassed by the present claims. Because Martinez et al. and Saez et al. do not discuss any non-steroidal gene switch activators other than diacylhydrazines, they do not provide any motivation to use DTBHIB as a gene switch activator or a reasonable expectation that DTBHIB can function as a gene switch activator.

The Examiner alleges that one of ordinary skill in the art would use DTBHIB in the gene switch activation methods of Martinez et al. or Saez et al. because Dhadialla teaches that DTBHIB binds the EcR and because the structure of DTBHIB is similar to the structure of diacylhydrazines.

Applicants respectfully disagree. In the Declaration of Robert E. Hormann Under 37 C.F.R. 1.132 attached hereto, Dr. Hormann, one of the co-inventors of the present application, provides data showing that there is little correlation between the ability of a compound to bind to the EcR and its ability to function as a gene switch activator (see Exhibits 2 and 3). Because of this lack of correlation, it is unpredictable whether an EcR-binding compound will also function as a gene switch activator. Thus, the teaching of Dhadialla et al. that DTBHIB can bind to the EcR does not provide a reasonable

expectation to one of ordinary skill in the art that DTBHIB will function in the gene switch activator systems of Martinez et al. and Saez et al.

In the Advisory Action mailed March 26, 2007, the Examiner alleges that Dhadialla et al. teach that DTBHIB is an EcR agonist with activity similar to RH-5849 and since RH-5849 is used as a gene switch activator, one would readily recognize that DTBHIB could also be an activator of EcR-based inducible gene expression systems. This is a misinterpretation of Dhadialla et al. What Dhadialla et al. actually teach is that the diacylhydrazine RH-5849 binds to the EcR and functions as a pesticide (page 548). There is no disclosure of the ability of RH-5849 to function as a gene switch activator. Dhadialla et al. further teach that DTBHIB has a similar potency to RH-5849 in terms of inducing morphological changes in Kc insect cells and competitively displacing tritiated PoA from the EcR (page 563). These activities relate to the ability of the compounds to bind the EcR and are not predictive of the ability to function as a gene switch activator. Thus, Dhadialla et al. do not teach or suggest anything that would provide an expectation that DTBHIB would function as a gene switch activator.

The Examiner also alleges in the Advisory Action that Mikitani (*Biochem. Biophys. Res. Commun. 227*:427 (1996)) teaches that DTBHIB has the ability to efficiently activate EcR-based inducible gene expression systems. Again, this is not an accurate interpretation of the reference. What Mikitani actually teaches is that exposing Kc insect cells which naturally express the EcR and which have been modified to contain an EcR-responsive reporter gene, to DTBHIB results in induced expression of the reporter gene. This experiment indicates that DTBHIB is capable of binding to the naturally expressed EcR in the cells and stimulating EcR-responsive pathways in the cell.

Because the cells do not contain an EcR-based gene switch (that is, a gene expression construct involving recombinant full length or chimeric EcR), the experiment does not provide any indication as to the ability of DTBHIB to function as a gene switch activator.

The Examiner alleges that it would have been obvious to derivatize DTBHIB into compounds encompassed by the present claims because the structure of DTBHIB is similar to the structure of the compounds of the present claims. Applicants assert that it is improper to use the compounds in the present claims to decide that it would have been obvious to make derivatives of DTBHIB that are encompassed by the present claims. This is hindsight analysis based on the teachings of the present specification and is absolutely prohibited. The teaching or suggestion to make the claimed combination must be found in the prior art, not in Applicants' disclosure.

Applicants point out that the structure of DTBHIB is not encompassed by the compounds of the present claims because it does not contain the right-hand carbonyl (ketone) group. Thus, even if one had tested DTBHIB in the gene expression system of Martinez *et al.* or Saez *et al.*, it would not anticipate or render obvious the present claims. The Examiner alleges that it would have been obvious to create derivatives of DTBHIB base on its central core structure and arrive at the compounds of the present claims. Applicants respectfully disagree. The amidoketone structure of the compounds of the present claims is the core structure of the compounds. Removal of the right-hand carbonyl group from the claimed compounds would likely eliminate most or all of the ability of the compounds to function as gene switch activators. In the Declaration of Robert E. Hormann Under 37 C.F.R. 1.132 attached hereto, Dr. Hormann provides data

showing that the right-hand carbonyl group in diacylhydrazine compounds (which corresponds structurally to the right-hand carbonyl group of the presently claimed compounds) is required for gene switch activity (see Exhibit 4). The data compares several diacylhydrazines with their corresponding compounds that are missing the carbonyl group. Many of the diacylhydrazines exhibited strong gene induction activity while the compounds without the carbonyl group are essentially inactive, indicating the necessity of the carbonyl group for activity. Because the right-hand carbonyl group in the diacylhydrazine compounds corresponds structurally to the right-hand carbonyl group in the claimed compounds, and DTBHIB does not contain a right-hand carbonyl group, one of ordinary skill in the art would have had no expectation that DTBHIB would function as a gene switch activator.

Because DTBHIB does not contain a right-hand carbonyl group, DTBHIB does not contain the same central core as the compounds of the present claims. Further, building a combinatorial library around the central core of DTBHIB would not produce the present compounds as the central core of DTBHIB does not contain the essential carbonyl moiety. Based on the lack of knowledge in the art and unpredictability regarding the structural requirements for EcR binding compounds and gene switch activators, there would have been no reasonable expectation by one of ordinary skill in the art that all or even some combinatorial derivatives of DTBHIB would act as an EcR binder, much less as an activator of an EcR-based gene switch. Mikitani supports the unpredictability of altering DTBHIB to produce active compounds. Mikitani teaches that the very closely related compound 3,5-di-tert-butyl-4-hydroxy-N-isopropylbenzamide, which differs from DTBHIB only by having an isopropyl side

chain instead of an isobutyl side chain, does not even bind to the EcR (page 428, first paragraph in Results section). Thus, even slight changes to the structure of DTBHIB can destroy EcR binding activity. In the absence of any knowledge regarding the ability of DTBHIB to act as a gene switch activator, it would have been even less obvious to derivatize DTBHIB with the hope of producing gene switch activators. Without a reasonable expectation of success, the claimed methods cannot be considered to be obvious over the cited art. At best, one of ordinary skill in the art might have considered it obvious to test DTBHIB in an EcR-based gene switch to see if the compound is capable of activating the gene switch. However, the Supreme Court recently held that an "obvious to try" standard is a proper standard for obviousness only "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions." *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, slip op. at 17 (2007). Here, there are an infinite number of derivatives of DTBHIB that could be made and there is no predictability as to which, if any, derivatives might function as gene switch activators. Thus, "obvious to try" is not a proper standard for obviousness in this instance.

Guan *et al.* does not make up for any of the deficiencies of Martinez *et al.*, Saez *et al.*, and Dhadialla *et al.*, as Guan *et al.* merely discuss the technique of using a core structure as a scaffold for varying substituents to look for compounds having an activity. Guan *et al.* do not discuss EcR ligands, gene expression systems, DTBHIB, or any factor related to the present claims. The ability to modify a compound in a combinatorial fashion does not provide any evidence of obviousness as it does not provide any expectation that any of the derivatives are likely to have a desired activity, particularly in

the present situation where the compound to be modified (DTBHIB) was not known in the art to have the desired activity (gene switch activation) in the first place.

The Examiner further alleges that the compounds disclosed in Michelotti *et al.* are very similar in structure to DTBHIB, and, even though the compounds act as fungicides and not pesticides, one of skill in the art would have been motivated to use them in the method of Martinez *et al.*

Applicants respectfully disagree. The Examiner has stretched the concept of obviousness far beyond its legal limits. The Examiner first alleges that it would have been obvious to use DTBHIB as a gene switch activator in the expression system of Martinez *et al.* and Saez et al. because DTBHIB appears to bind the EcR. As discussed above, the fact that DTBHIB appears to bind the EcR provides no expectation that the compound will function as a gene switch activator. The Examiner next goes one step further and alleges that it would have been obvious to use the compound of Michelotti *et al.* instead of DTBHIB as a gene switch activator because the compounds have similar structures. This allegation is baseless. There is absolutely no teaching, motivation or suggestion in Michelotti *et al.* that the compounds disclosed therein function as pesticides or have any ability to bind the EcR. The only teaching in Michelotti *et al.* is that the compounds act as fungicides and are non-toxic to plants. By the Examiner's reasoning, any compound in the world that is similar to DTBHIB is (1) expected to bind the EcR; and (2) therefore expected to function as an activator of EcR-based gene expression systems. As discussed above, both of these expectations are unsupported by the cited art or by the general knowledge in the art.

Furthermore, a *prima facie* case of obviousness based on close structural similarity between chemical compounds is appropriately made only when the compounds are exceedingly close in structure such that that one would expect the compounds to have similar properties. *See In re Payne*, 606 F.2d 303, 313, 203 U.S.P.Q. 245, 254 (CCPA 1979). Examples of sufficient structural similarity cited in the M.P.E.P. are position isomers (compounds having the same radicals in physically different positions on the same nucleus) and homologs (compounds differing regularly by the successive addition of the same chemical group, *e.g.*, by -CH_2- groups), although it is also stated that prior art structures do not have to be true isomers or homologs of each other to render structurally similar compounds *prima facie* obvious. *See* M.P.E.P. 2144.09. However, the M.P.E.P. clearly states that a rejection based on structural similarity occurs in the situation where a prior art compound is known to have a particular activity and the claimed compound is so similar that one would expect it to have the same activity as the prior art compound.

Here, compounds disclosed by Michelotti *et al.* and DTBHIB do not share sufficient close structural similarity to have an expectation of similar properties as they differ in significant structures such as a carbonyl group which would be expected to impart different activities to a compound. The same is true for DTBHIB as compared to diacylhydrazine EcR ligands. More importantly, DTBHIB was not known in the art to function as a gene switch activator. Even if one believed that DTBHIB is structurally similar to the Michelotti compounds or to diacylhydrazine ligands (which it is not), there was no known gene switch activity in DTBHIB that would provide an expectation that a

structurally similar compound had the same gene switch activity. Thus, a *prima facie* case of obviousness has not been made.

In the Declaration of Robert E. Hormann Under 37 C.F.R. 1.132 attached hereto, Dr. Hormann provides data showing that three compounds encompassed by the structure disclosed in Michelotti et al. were synthesized and tested in a gene switch activation assay (see compounds RG-108841, RG-108858, RG-109043). Additionally, more than one hundred other compounds that are similar in structure to the compounds of Michelotti *et al.* (haloalkyl group on the right side, aryl group on the left side) were synthesized and tested for activity. None of these compounds were found to be able to significantly induce gene expression in the assay (see Exhibit 5). Thus, the compounds described in Michelotti *et al.* are unlikely to function as gene switch activators. The present claims have been amended such that they do not encompass compounds having a haloalkyl group in the R^4 position as required in the compounds of Michelotti *et al.* Because of the amendments to the claims to exclude compounds disclosed in Michelotti *et al.*, Michelotti *et al.* in combination with the other cited references cannot render the present claims obvious.

It is respectfully requested that the rejection of claims 6-17 under 35 U.S.C. § 103(a) be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be

withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert A. Schwartzman, Ph.D.
Attorney for Applicants
Registration No. 50,211

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
670936_1.DOC